CONCISE COMMUNICATION

Neurocognition and quality of life after reinitiating antiretroviral therapy in children randomized to planned treatment interruption

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Objective: Understanding the effects of antiretroviral treatment (ART) interruption on neurocognition and quality of life (QoL) are important for managing unplanned interruptions and planned interruptions in HIV cure research.

Design: Children previously randomized to continuous (continuous ART, $n = 41$) vs. planned treatment interruption (PTI, $n = 47$) in the Pediatric European Network for Treatment of AIDS (PENTA) 11 study were enrolled. At study end, PTI children resumed ART. At 1 and 2 years following study end, children were assessed by the coding, symbol search and digit span subtests of Wechsler Intelligence Scale for Children (6–16 years old) or Wechsler Adult Intelligence Scale (≥17 years old) and by Pediatrics QoL questionnaires for physical and psychological QoL. Transformed scaled scores for neurocognition and mean standardized scores for QoL were compared between arms by *t*-test and Mann–Whitney U test, respectively. Scores indicating clinical concern were compared (<7 for neurocognition and <70 for QoL tests).

Results: Characteristics were similar between arms with a median age of 12.6 years, $CD4^+$ of 830 cells/μl and HIV RNA of 1.7 $\log_{10}$copies/ml. The median cumulative ART exposure was 9.6 in continuous ART vs. 7.7 years in PTI ($P = 0.02$). PTI children had a median of 12 months off ART and had resumed ART for 25.2 months at time of first assessment. Neurocognitive scores were similar between arms for all tests. Physical and psychological QoL scores were no different. About 40% had low neurocognitive and QoL scores indicating clinical concern.

Conclusion: No differences in information processing speed, sustained attention, short-term memory and QoL functioning were observed between children previously randomized to continuous ART vs. PTI in the PENTA 11 trial.

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Introduction

Severe forms of HIV-associated brain insult or HIV encephalopathy have fortunately become less common since the widespread use of antiretroviral therapy (ART). However, milder but static forms of neurocognitive impairment (NCI) afflict up to half of children living with HIV [1–3], and may compromise their successful transition into adulthood. Advanced HIV disease and unsuppressed HIV viremia are predictors of poor neurocognition as well as quality of life (QoL) [4–6]. Therefore, ART interruption may negatively impact these factors.

Here we capitalize on the unique opportunity to assess neurocognition and QoL in children who were randomized to continuous ART vs. $CD4^+$-guided planned treatment interruption (PTI) in the Pediatric European Network for Treatment of AIDS (PENTA) 11 trial [7]. At the end of the trial, PTI children were advised to reinitiate ART and after 2 years of ART resumption, similar clinical, immunological, and virological outcomes were observed between arms [8]. However, neurocognition and QoL have not yet been compared. As the Strategies for Management of Antiretroviral Therapy study in adults showed excessive risks for adverse outcomes with PTI even after ART was reinitiated [9], we conducted this substudy to compare neurocognition and QoL at 1 and 2 years following the end of the PENTA 11 study. Although PTI is not a recommended treatment strategy, this study is relevant to the treatment of HIV-infected children because unplanned ART interruption is not infrequent, particularly in adolescents [10], and treatment interruption may be a critical component of future HIV cure research [11]. Understanding the effects of ART interruption on neurocognition and QoL could inform monitoring and intervention of these children.

Methods

This is a substudy of the PENTA 11 trial (ISRCTN36694210) in which virally suppressed HIV-infected children were randomized to either 72 weeks of continuous ART vs. PTI as previously described [7]. At trial end in May 2008, ART was reinitiated in PTI children and routine HIV care data were collected in both arms for 5 years as part of the long-term cohort study [8]. In addition, children were offered enrollment in this substudy with annual neurocognitive and QoL assessments; here we include data from years 1 and 2. The neurocognitive measures were three subscales (coding, symbol search, and digit span) from either the Wechsler Intelligence Scale for Children (WISC IV for those aged 6 to $<$17 years old) or the Wechsler Adult Intelligence Scale (WAIS IV for those aged $\geq$17 years old). Scaled scores rather than raw scores are reported as these are corrected for age and are comparable for the WISC and WAIS scales. The coding and symbol search subscales assess speed of information processing and sustained attention, whereas digit span assesses short-term memory. These tests were selected because they evaluate cognitive domains that have been reported as most vulnerable to the effects of HIV (short-term memory, attention, and processing speed) and they depend less on verbal or language comprehension, therefore, maximizing data fidelity across ethnic and language contexts. Additionally, participating sites had experience administering these tests.

Children and carers were also separately asked to complete Pediatrics Quality of Life (PedsQL) questionnaires [12]. These scales contain 23 items about physical, emotional, social, and school functions. There are age appropriate versions from 5 to more than 18 years old. All items were rated on a 5-point rating scale and scores were then standardized on 100-point scale in which higher scores reflected better QoL. Carers gave their consent and consent/assent was obtained from children according to local practices. The study was approved by Ethics Committees for all participating sites.

Data Analysis

The neurocognitive raw scores were transformed into normative scaled scores; means on each scale were computed and the number of children with a scaled score below seven was obtained. This cutoff represents scores significantly below the test mean compared with others of the same age. On the PedsQL, overall mean scores for physical and psychosocial functions were computed, as were scores of 70 or less on any scale. This cutoff has been used to indicate clinical concern [13].

Differences between mean continuous ART and PTI arm scores were tested for each neurocognitive test and QoL assessment score, using an independent samples *t*-test and Mann–Whitney U test, respectively. This outcome was analyzed using exact logistic regression to test for differences between the two arms, with the analysis adjusted for sex, Centers for Disease Control and Prevention (CDC) class C status, nadir CD4%, and continent. An identical sensitivity analysis was also performed by excluding children with HIV encephalopathy.

Results

Of 101 children (51 continuous ART and 50 PTI) from the PENTA 11 trial who were eligible for inclusion, 88 children from seven countries participated in this substudy (41 continuous ART and 47 PTI). Table 1 shows the characteristics of the children at time of their

Table 1. Characteristics of children at time of their first neurocognitive and quality of life assessment.

	Total ($n=88$)[a]	Children in CT arm ($n=41$) (73% of all children in CT arm)	Children in PTI arm ($n=47$) (84% of all children in PTI arm)	*P* value
Median (IQR) age	12.6 (9.6–15.2)	12.9 (10.1–15.3)	12.6 (9.5–14.4)	0.77
Women, *n* (%)	50 (57%)	25 (61%)	25 (53%)	0.46
Ethnicity, *n* (%)				
White	33 (38%)	14 (34%)	19 (40%)	0.72
Black	22 (25%)	9 (22%)	13 (28%)	
Asian/Thai	22 (25%)	12 (29%)	10 (21%)	
Other	11 (13%)	6 (15%)	5 (12%)	
CDC clinical stage C	25 (28%)	16 (39%)	9 (19%)	0.04
Weight for age Z score	−0.3 (−1.2 −0.8)	−0.3 (−1.5 −1.1)	−0.3 (−1.2 −0.4)	0.75
Height for age Z score	−0.5 (−1.6 −0.5)	−0.4 (−1.7 −0.5)	−0.5 (−1.4 −0.5)	0.74
Median (IQR) nadir CD4%	17 (12–24)	18 (12–28)	16 (11–22)	0.08
Median (IQR) CD4%	36 (32–40)	38 (34–40)	34 (29–40)	0.03
Median (IQR) $CD4^+$ cell count (cells/μl)	830 (693–1058)	866 (750–1065)	814 (630–981)	0.27
Median (IQR) HIV RNA (log_{10}copies/ml)	1.7 (1.6–1.7)	1.7 (1.6–1.7)	1.7 (1.7–2.0)	0.08
Current ART regimen, *n* (%)				
Efavirenz	26 (30%)	11 (27%)	15 (32%)	0.60
Nevirapine	24 (27%)	13 (32%)	11 (23%)	
Boosted PI	6 (7%)	3 (7%)	3 (6%)	
Unboosted PI	21 (24%)	10 (24%)	11 (23%)	
PI and NNRTI	5 (6%)	3 (7%)	2 (4%)	
Off ART	4 (5%)	0 (0%)	4 (9%)	
Other	2 (2%)	1 (2%)	1 (2%)	
Median (IQR) cumulative ART exposure (years)	8.3 (6.0–11.0)	9.6 (7.1–12.4)	7.7 (5.2–10.5)	0.02
Median (IQR) cumulative time of ART interruption (months)	–	Not applicable	12.0 (7.0–18.2)	
Median (IQR) time since ART interruption (months)	–	Not applicable	25.2 (18.9–31.2)	

These characteristics were collected one year after the main PENTA 11 trial ended and children had their first neurocognitive and quality of life assessments. ART, antiretroviral therapy; CT, continuous antiretroviral treatment; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PTI, partial treatment interruption.
[a]Participating sites in: France, Ireland, Italy, Poland, Spain, Switzerland, and United Kingdom.

first assessment 1 year after the main trial ended. Both the continuous ART and PTI groups were similar in age, sex, ethnicity, and HIV-related factors except that there tended to be more CDC grade C illnesses in the continuous ART arm ($P=0.05$) and CD4% was slightly lower in PTI arm although very similar at 2 years [8]. Two continuous ART children had HIV encephalopathy but none in the PTI arm. The cumulative time on ART was longer in the continuous ART arm. The PTI children had about 1 year of ART interruption and had been back on ART for about 2 years at the time of their first neurocognitive and QoL assessment.

Table 2 shows the neurocognitive and PedsQL outcomes. The mean scaled scores and the proportion with low scaled scores for all three neurocognitive tasks were not significantly different between arms for both years 1 and 2. In year 1, 38% had scaled score below seven on at least one test, with low scores observed in 18% for symbol search, 20% for coding, and 20% for digit span. In year 2, the scaled scores and proportion of children with low scores were similar between arms. There were no significant changes between year 1 and 2 for all neurocognitive subscales except for a trend toward fewer children having low scores in year 2 for symbol search and digit span.

The mean scores on the physical or psychological scales of the PedsQL were similar for those in the continuous ART and PT arms for the carer reports for years 1 and 2; physical but not psychological scores for the child were lower in the PTI arm in year 2 only (Table 2). The proportions of children with low scores, that is, less than 70, on either the physical or the psychological scale were not different between arms. Combining the two arms found the percentage of all children scoring less than 70 in year 1 to be 14% for the physical scale and 28% for the psychosocial scale; results were similar in year 2 (Table 2). Carers reported a higher level of concern in most areas than the children. The neurocognitive and QoL outcomes did not change when children with HIV encephalopathy were excluded.

Discussion

Although continuous ART is the standard of care, adherence to ART is not easy and clinicians are faced with managing unplanned ART interruptions in children and teenagers [10,14]. The randomized PENTA 11 study offers a unique opportunity to evaluate if ART interruption guided by $CD4^{+}$ had adverse neurocognitive

Table 2. Neurocognitive and quality of life outcomes.

	Neurocognitive outcomes			
	Total ($n=88$)	Children in CT arm ($n=41$)	Children in PTI arm ($n=47$)	*P* value
Neurocognitive tasks		Mean scaled score (SD)	Mean scaled score (SD)	
Symbol search				
Year 1	9.2 (3.0)	8.9 (2.9)	9.6 (3.0)	0.28
Year 2	9.6 (2.8)	9.8 (3.1)	9.4 (2.5)	0.48
Coding				
Year 1	8.8 (3.1)	8.4 (3.1)	9.2 (3.2)	0.22
Year 2	8.7 (2.8)	8.7 (3.0)	8.8 (2.7)	0.86
Digit span				
Year 1	9.5 (3.2)	9.1 (3.2)	9.9 (3.3)	0.29
Year 2	9.5 (3.0)	9.2 (2.8)	9.8 (3.2)	0.40
Neurocognitive tasks		*N* with mean scaled score <7 (%)	*N* with mean scaled score <7 (%)	
Symbol search				
Year 1	15 (18)	10 (25)	5 (12)	0.14
Year 2	10 (13)	5 (14)	5 (13)	>0.99
Coding				
Year 1	17 (20)	9 (23)	8 (18)	0.59
Year 2	17 (22)	7 (18)	10 (26)	0.60
Digit span				
Year 1	17 (20)	10 (24)	7 (16)	0.28
Year 2	11 (14)	7 (18)	4 (10)	0.25

	Quality-of-life outcomes			
		Children in CT arm ($n=41$) (73% of all children in CT arm)	Children in PTI arm ($n=47$) (84% of all children in PTI arm)	*P* value
PEDsQL – child report scales		Mean score (SD)	Mean score (SD)	
Physical functioning				
Year 1	82.8 (14.7)	86.1 (10.6)	80.0 (17.1)	0.15
Year 2	86.0 (13.9)	89.6 (11.3)	82.5 (15.4)	0.04
Psychosocial functioning				
Year 1	74.9 (15.7)	75.3 (16.3)	74.5 (15.4)	0.77
Year 2	78.2 (12.4)	79.5 (10.8)	77.0 (13.8)	0.44
PEDsQL – carer report scales				
Physical functioning				
Year 1	77.9 (20.1)	79.3 (20.4)	76.6 (20.1)	0.40
Year 2	80.6 (21.1)	81.2 (21.8)	80.1 (20.7)	0.51
Psychosocial functioning				
Year 1	72.0 (17.0)	70.6 (17.7)	73.3 (16.3)	0.46
Year 2	73.4 (15.4)	73.8 (14.0)	73.0 (16.7)	0.95
PEDsQL – child report scales		*N* with mean score <70 (%)	*N* with mean score <70 (%)	
Physical functioning				
Year 1	11 (14)	2 (5)	9 (21)	0.17
Year 2	11 (14)	3 (8)	8 (21)	0.48
Psychosocial functioning				
Year 1	22 (28)	10 (27)	12 (28)	>0.99
Year 2	17 (22)	7 (19)	10 (26)	0.66
PEDsQL – carer report scales				
Physical functioning				
Year 1	24 (29)	11 (28)	13 (31)	>0.99
Year 2	18 (25)	8 (24)	10 (26)	>0.99
Psychosocial functioning				
Year 1	30 (37)	17 (43)	13 (31)	0.29
Year 2	25 (35)	12 (35)	13 (34)	>0.99

CT, continuous antiretroviral treatment; PTI, partial treatment interruption

and QoL consequences. Here we demonstrated that children who had interrupted ART for about a year and subsequently resumed ART for an average of 2 years performed similarly on information processing speed, sustained attention and short-term memory compared with those who had not interrupted therapy. Almost 40% had scores below those of healthy children, illustrating the chronic stable NCI that continues to be prevalent in children living with HIV [1,3]. QoL scores were also similar between randomized arms but approximately one-third of children had scores in the range that indicate clinical concern.

HIV affects the brain directly by infecting resident macrophages and astrocytes, and indirectly, by triggering inflammatory responses – both processes could be more pronounced in the immature brain [15,16]. HIV proteins such as gp120, Tat, Nef, and Vpr can also be neurotoxic by causing neuronal cell death when released from HIV-infected cells, possibly leading to functional impairment [17]. Consequently, the magnitude and duration of HIV viremia predicts NCI [18] leading to our concern of adverse consequences in the interrupted arm of this study. No studies have investigated the effects of ART interruption on neurocognition and QoL but inferences could be drawn from those that evaluate timing of ART on these factors. The Pediatric Randomized to Early versus Deferred Initiation in Cambodia and Thailand study randomized children who were about 6 years old to initiating ART at $CD4^+$ 15–24% vs. deferring until $CD4^+$ less than 15% and did not find differences in intelligent quotients and psychomotor performance nor QoL scores after 3 years [19,20]. However, the Children with HIV Early Antiretroviral Therapy study observed poorer neurocognitive outcomes in infants who were randomized to defer ART until $CD4^+$ ~25% vs. those who initiated before 3 months of age [21]. These data suggest that brain insult from HIV likely occurs early during infancy [22,23]; therefore, delayed ART or ART interruption might not have an apparent effect on brain functioning in older children. A consistent finding across studies remains that a significant proportion of children with HIV perform poorer on neurocognitive and QoL tests [4–6]. The impaired information processing, sustained attention and short-term memory observed in our patients could potentially have long-term adverse consequences on school and social functioning [24]. This is further supported by the low scores on these subscales of the QoL in our children (data not shown).

Our study is limited by the lack of assessment at baseline or during ART interruption; therefore, any prior differences between arms cannot be accounted for. Because a comprehensive battery of assessments was not performed, subtle differences between arms could have been missed. Importantly, psychosocial and environmental data relevant to neurocognition and QoL were not collected. The duration of follow-up was relatively short, and NCI may become apparent later when children are older and required to engage in complex tasks. More of the continuous ART arm children were in the CDC C advanced HIV stage at the beginning of the main trial (64 vs. 32% in PTI), and fewer (73%) participated in the neurocognitive substudy compared with 84% of PTI children. This may have contributed to the favorable outcome observed in the PTI arm. However, both arms experienced no deaths or CDC C events during the entire follow-up duration.

The HIV field was reinvigorated with the news of HIV remission in the Mississippi baby [25], which sadly turned out not to be sustained [26]. In HIV cure research, intensively monitored antiretroviral pause (iMAP) is being employed as the ultimate test for a cure. iMAP is defined as a pause in ART that is accompanied by frequent monitoring for viral load rebound followed by a prompt resumption of treatment if rebound occurs [27]. Several studies involving administration of therapeutic vaccines with and without iMAP are being planned [28,29]. Our study provides reassuring information that no short-term neurocognitive and QoL effects from treatment interruption were observed. However, as these cure studies progress and include early treated children who may have preserved cognitive function, the effects of treatment interuption on neurocognition should be closely observed.

Finally, millions of children with HIV around the world are entering adolescence. Future research should focus on understanding their development of executive function including decision-making, planning, and self-regulation by taking into account the psychosocial and environmental contexts [30,31]. It will be important to leverage opportunities to study neurocognitive functioning in the context of treatment trials including pediatric cure trials to optimize performance and successful transition of youth with HIV into the work force.

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D.M.G., A.C., and D.M. designed and provided oversight of the study. J.A., J.T.R.A., J.T.C., G.M., V.B., A.C., S.K., S.M., and D.M.G. conducted the study and provided scientific input on the study design and data interpretation. T.C. performed the analysis. D.M. directed the neurocognitive assessment and analysis. J.A. authored the first draft of the manuscript and finalized it with input from all coauthors.

Conflicts of interest

There are no conflicts of interest.

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